

CLAIMS

1. Process for the preparation of N-acyl-(epi)K5-amine-O-versulfate-derivatives and of its chemically or pharmaceutically acceptable salts, characterized in that
 - (a) an (epi)K5-N-sulfate-derivative, in acidic form, is treated with a tertiary or quaternary organic base, letting the reaction mixture to stand for a time period of 30-60 minutes, maintaining the pH of the solution at a value of approximately 7 and its salt is isolated with said organic base;
 - (b) said salt of organic base of said (epi)K5-N-sulfate-derivative is treated with an O-sulfation reagent in the conditions of O-versulfation;
 - (c) the (epi)K5-amine-O-versulfate-derivative thus obtained is treated with a functional derivative of a (C₂-C₄) carboxylic acid, the N-acyl-(epi)K5-amine-O-versulfate-derivative is isolated.
2. Process according to claim 1, characterized in that said N-acyl-(epi)K5-N,O-versulfate-derivative is isolated in sodium salt form and optionally transformed into another chemically or pharmaceutically acceptable salt.
3. Process according to anyone of claims 1 and 2, characterized in that, in step (a) tetrabutylammonium hydroxide is used as an organic base.
4. Process according to anyone of claims from 1 to 3, characterized in that, in step (b) the O-versulfation is carried out in dimethylformamide utilizing 2-4 moles of O-sulfation reagent per available OH per disaccharide at a temperature of 40-60°C for 15-20 hours.
5. Process according to anyone of claims from 1 to 4, characterized in that as starting material an (epi)K5-N-sulfate-derivative is used having

a mean molecular weight from approximately 1,000 to approximately 25,000.

6. Process according to anyone of claims from 1 to 5, characterized in that said starting material is 40-60% C5-epimerized.

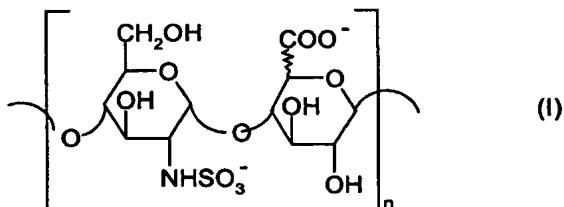
7. Process according to anyone of claims from 1 to 6, characterized in that said starting material has a mean molecular weight from approximately 1,500 to approximately 25,000.

8. Process according to claim 7, characterized in that said starting material has a mean molecular weight between 10,000 and 25,000.

9. Process according to claim 7, characterized in that said starting material has a mean molecular weight from approximately 1,500 to approximately 12,000.

10. Process according to claim 9, characterized in that said starting material has a mean molecular weight from approximately 1,500 to approximately 8,000.

11. Process according to claim 5, characterized in that as starting material an (epi)K5-N-sulfate-derivative is used consisting of a chain mixture in which at least 90% of said chains have the formula I



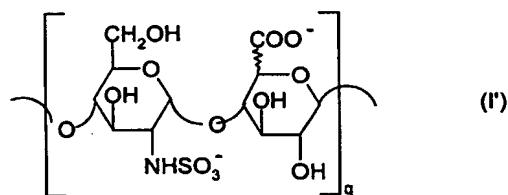
in which the glucuronic units/iduronic units ratio is from 100/0 to 40/60, n is an integer from 2 to 100 and the corresponding cation is chemically or pharmaceutically acceptable.

12. Process according to claim 11, characterized in that said starting material is consisting of a chain mixture in which at least 90% of said chains have the formula I, in which the uronic units are 40-60%

consisting of iduronic acid.

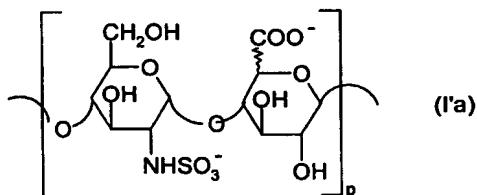
13. Process according to claim 11, characterized in that said starting material is a Imw-(epi)K5-N-sulfate consisting of a chain mixture in which at least 90% of said chains have the formula I in which the uronic units are all consisting of glucuronic acid or are 40-60% consisting of iduronic acid, n is a integer from 3 to 15 and the corresponding cation is chemically acceptable.

14. Process according to claim 11, characterized in that said starting material is a Imw-(epi)K5-N-sulfate consisting of a chain mixture in which at least 90% of said chains have the formula I'



in which the uronic units are 100% consisting of glucuronic acid or 60-40% of glucuronic acid and 40-60% of iduronic acid, q is a integer from 2 to 20 and the corresponding cation is chemically or pharmaceutically acceptable.

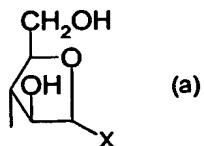
15. Process according to claim 11, characterized in that said starting material is a Imw-(epi)K5-N-sulfate consisting of a chain mixture in which the preponderant species has the formula I'a



in which the uronic units are 100% consisting of glucuronic acid or 60-40% glucuronic and 40% to 60% of iduronic acid, p is a integer from 4 to 8.

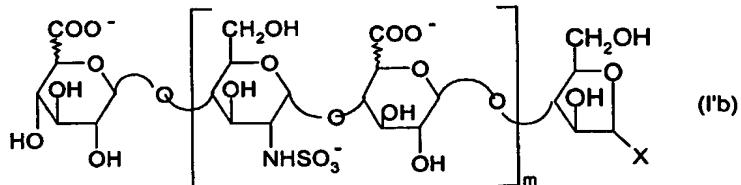
16. Process according to anyone of claims from 5 to 15, characterized in that said starting material is a lmw-(epi)K5-N-sulfate obtained by nitrous depolymerization of the corresponding (epi)K5-N-sulfate and subsequent reduction.

17. Process according to claim 16, characterized in that said starting LMW-(epi)K5-N-sulfate contains, at the reducing end of the majority of the chains in said chain mixture, a 2,5-anhydromanno unit of structure (a)



in which X represents a hydroxymethyl group.

18. Process according to anyone of claims 16 and 17, characterized in that as starting material a lmw-(epi)K5-N-sulfate is used consisting of chain mixtures in which the preponderant species is a compound of formula I'b



in which X is hydroxymethyl, m is 4, 5 or 6, the corresponding cation is one chemically or pharmaceutically acceptable ion, the uronic units are all of glucuronic acid or the glucuronic and iduronic units are present alternately, starting with a glucuronic or iduronic unit.

19. Process according to anyone of claims from 1 to 18, characterized in that said starting (epi)K5-N-sulfate-derivative is utilized in sodium salt form.

20. An N-acyl-(epi)K5-amine-O-versulfate-derivative obtainable according to the process of claims from 1 to 19.

21. An N-acyl-(epi)K5-amine-O-versulfate-derivative according to claim 20 in salt form of an alkaline metal or alkaline-earth metal, of ammonium, (C₁-C₄)tetraalkylammonium, aluminum or zinc.

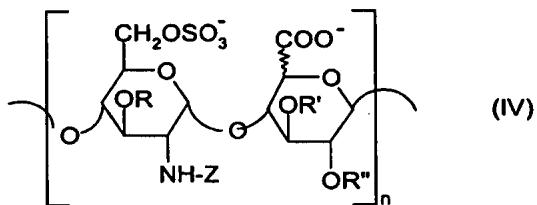
22. An N-acyl-epiK5-amine-O-versulfate-derivative, in which acyl is a (C₂-C₄)acyl, having an iduronic acid content of 20-60%, a mean molecular weight from approximately 2,000 to approximately 45,000 and a sulfation degree of at least 3.4, or one of its chemically or pharmaceutically acceptable salts.

23. An N-acyl-epiK5-amine-O-versulfate-derivative according to claim 22, whose mean molecular weight is between approximately 15,000 and approximately 45,000.

24. An N-acyl-epiK5-amine-O-versulfate-derivative according to claim 22, whose mean molecular weight is between approximately 4,500 and approximately 8,500.

25. An N-acyl-epiK5-amine-O-versulfate-derivative according to anyone of claims from 22 to 24, characterized in that said degree of sulfation is from 3.4 to 3.8.

26. An N-acyl-epiK5-amine-O-versulfate-derivative consisting of chain mixtures in which at least 90% of said chains have the formula IV

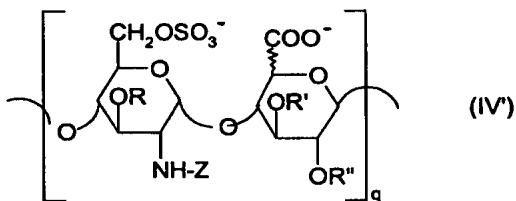


in which the uronic units are 20-60% consisting of iduronic acid, n is a integer from 2 to 100, R, R' and R" are hydrogen or SO₃⁻, Z is(C₂-C₄)acyl, the degree of sulfation is at least 3.4 and the corresponding cation is chemically or pharmaceutically acceptable.

27. An N-acyl-epiK5-amine-O-versulfate-derivative according to

claim 26, characterized in that it consists of a chain mixture in which at least 90% of said chains have the formula IV in which the uronic units are 40-60% consisting of iduronic acid, n is a integer from 3 to 100, with a mean molecular weight from approximately 2,000 to approximately 45,000, R is at least 40% SO_3^- , R' and R" are both SO_3^- or one is hydrogen and the other is 5-10% SO_3^- in monosulfate glucuronic acid and 10-15% SO_3^- in monosulfate iduronic acid and the corresponding cation is chemically or pharmaceutically acceptable.

28. An N-acyl-epiK5-amine-O-versulfate-derivative according to anyone of claims 26 and 27, characterized in that it is a Imw-N-acyl-epiK5-O-versulfate consisting of a chain mixture in which at least 90% of said chains have the formula IV'

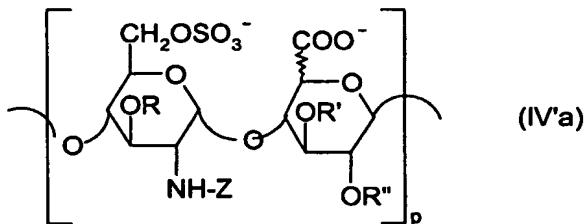


in which q is a integer from 2 to 20, R, R' and R" represent hydrogen or an SO_3^- group for a degree of sulfation from 3.55 to 4, Z is $(\text{C}_2\text{-}\text{C}_4)\text{acyl}$, and the corresponding cation is chemically or pharmaceutically acceptable.

29. A Imw-N-acyl-epiK5-O-versulfate according to claim 28, characterized in that in said chain mixture of formula IV' the uronic units are 50-55% consisting of iduronic acid, R is at least 40% SO_3^- , R' and R" are both SO_3^- or one is hydrogen and the other is 5-10% SO_3^- in glucuronic acid and 10-15% SO_3^- in iduronic acid, q is a integer from 3 to 15, with a mean molecular weight from approximately 4,500 to approximately 9,000 and the corresponding cation is chemically or pharmaceutically acceptable.

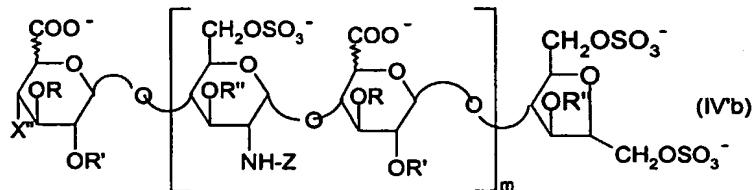
30. A Imw-N-acyl-epiK5-O-versulfate according to anyone of claims

28 and 29, characterized in that it consists of a chain mixture in which the preponderant species is a compound of formula IV'a



in which p is an integer from 4 to 8, R, R' and R'' are hydrogen or an SO₃⁻ group for a degree of sulfation from 3.55 to 4, Z is (C₂-C₄)acyl, and the corresponding cation is chemically or pharmaceutically acceptable.

31. A Imw-N-acyl-epiK5-O-versulfate according to claim 30, characterized in that said preponderant species is a compound of formula IV'b



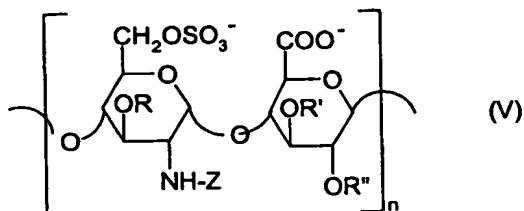
in which R, R' and R'' are hydrogen or SO₃⁻, Z is (C₂-C₄)acyl, X is OH or OSO₃⁻, m is 4, 5 or 6, for a degree of sulfation from 3.55 to 4, the uronic units are present alternately, starting with a glucuronic or iduronic unit, and the corresponding cation is chemically or pharmaceutically acceptable.

32. A Imw-N-acyl-epiK5-O-versulfate according to any of claims from 22 to 31 in which the substituent (C₂-C₄)acyl is selected from the group consisting of acetyl, (2-carboxy)acetyl, (2-methoxycarbonyl)acetyl, (2-ethoxycarbonyl)acetyl, propionyl, (3-carboxy)propionyl, N-(3-methoxycarbonyl)propionyl and (3-ethoxycarbonyl)propionyl.

33. An N-acyl-epiK5-amine-O-versulfate-derivative according to anyone of claims from 22 to 32, characterized in that said salt or

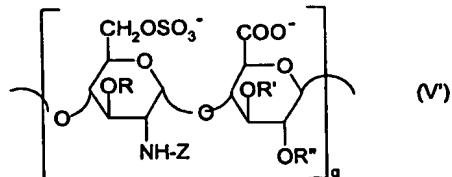
corresponding cation is an alkaline metal or alkaline-earth metal, of ammonium, (C₁-C₄)tetraalkylammonium, aluminum or zinc.

34. An N-acyl-K5-amine-O-versulfate-derivative consisting of a chain mixture in which at least 90% of said chains have the formula V



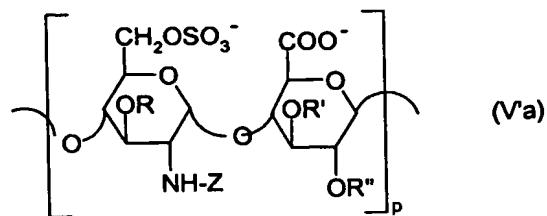
in which n is a integer from 2 to 100, Z is (C₂-C₄)acyl, R, R' and R'' are hydrogen or SO₃⁻, the degree of sulfation is at least 2.2, and the corresponding cation is chemically or pharmaceutically acceptable.

35. An N-acyl-K5-amine-O-versulfate-derivative according to claim 34, characterized in that it is a Imw-N-acyl-K5-amine-O-versulfate consisting of a chain mixture in which at least 90% of said chains have the formula V'



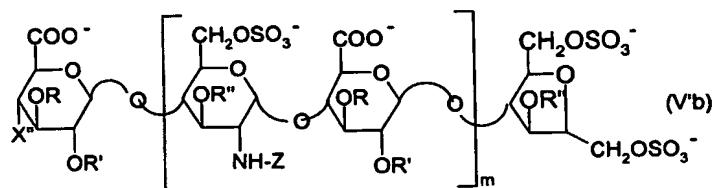
in which q is a integer from 2 to 20, Z is (C₂-C₄)acyl, R, R' and R'' represent hydrogen or an SO₃⁻ group for a degree of sulfation from 2.2 to 3, and the corresponding cation is chemically or pharmaceutically acceptable.

36. A Imw-N-acyl-K5-amine-O-versulfate according to claim 35, characterized in that it consists of a chain mixture in which the preponderant species is a compound of formula V'a



in which p is a integer from 4 to 8, Z is (C₂-C₄)acyl, R, R' and R" represent hydrogen or an SO₃⁻ group for a degree of sulfation from 2.2 to 3, and the corresponding cation is chemically or pharmaceutically acceptable.

37. A Imw-N-acyl-K5-amine-O-versulfate according to claim 36, characterized in that said preponderant species is a compound of formula V'b



in which Z is (C₂-C₄)acyl, R, R' and R" are hydrogen or SO₃⁻, X" is OH or OSO₃⁻, for a degree of sulfation from 2.2 to 3, m is 4, 5 or 6 and the corresponding cation is one chemically or pharmaceutically acceptable ion.

38. An N-acyl-K5-amine-O-versulfate-derivative according to anyone of claims from 34 to 37, characterized in that said degree of sulfation is from 2.3 to 3.

39. An N-acyl-K5-amine-O-versulfate-derivative according to claim 38, characterized in that said degree of sulfation is from 2.5 to 3.

40. An N-acyl-K5-amine-O-versulfate-derivative according to claim 39, characterized in that said degree of sulfation is from 2.7 to 2.9.

41. An N-acyl-K5-amine-O-versulfate-derivative according to anyone of claims from 34 to 40, in which the substituent (C₂-C₄)acyl is different

from acetyl.

42. An N-acyl-K5-amine-O-versulfate-derivative according to anyone of claims from 34 to 40, in which the substituent (C₂-C₄)acyl is acetyl, having a degree of sulfation of 2.7-2.9.

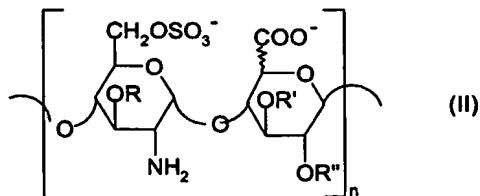
43. An N-acyl-K5-amine-O-versulfate-derivative according to claim 42, having a degree of sulfation of approximately 2.8.

44. An N-acyl-K5-amine-O-versulfate-derivative according to anyone of claims from 34 to 43, characterized in that said salt or corresponding cation is an alkaline metal or alkaline-earth metal, of ammonium, (C₁-C₄)tetraalkylammonium, aluminum or zinc.

45. Pharmaceutical composition including, as one of its active ingredients, an (epi)K5-amine-O-versulfate-derivative or one of its pharmaceutically acceptable salts, obtainable by the process according to steps (a) and (b) of the claim 1, isolated in sodium salt form and optionally transformed into another pharmaceutically acceptable salt, in mixture with a pharmaceutical excipient.

46. Composition according to claim 45, characterized in that said active ingredient is an (epi)K5-amine-O-versulfate-derivative having a mean molecular weight from approximately 4,500 to approximately 40,000.

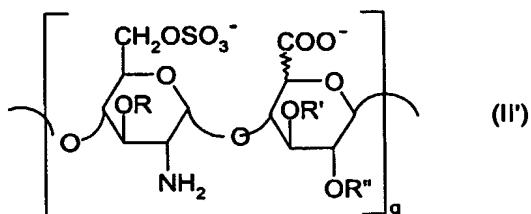
47. Pharmaceutical composition according to anyone of claims 45 and 46, in which said active ingredient is an (epi)K5-amine-O-versulfate-derivative consisting of a chain mixture in which at least 90% of said chains have the formula II



in which n is a integer from 2 to 100, R, R' and R" are hydrogen or SO₃⁻.

the ionic units are all of glucuronic acid, for a degree of sulfation from 2.2 to 3, or are 20-60% consisting of iduronic acid, for a sulfation degree of at least 3.4, and the corresponding cation is pharmaceutically acceptable.

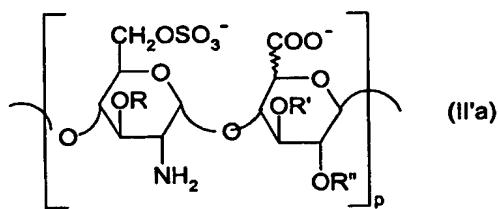
48. Pharmaceutical composition according to claim 47, characterized in that said active ingredient is a LMW-epiK5-amine-O-versulfate consisting of a chain mixture in which at least 90% of said chains have the formula II'



in which q is an integer from 2 to 20, R, R' and R'' are hydrogen or SO_3^- , the ionic units are 20-60% comprised, preferably 40-60%, of iduronic acid, for a degree of sulfation from 3.55 to 4.

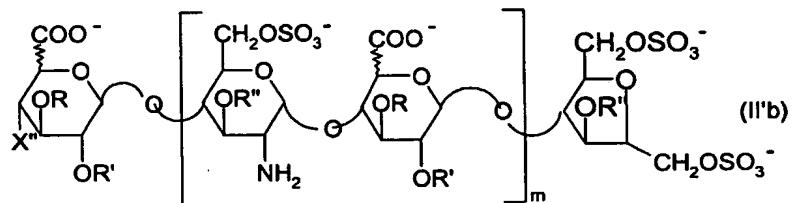
49. Pharmaceutical composition according to claim 48, characterized in that, in said chain mixture of formula II', the ionic units are 40-60% consisting of iduronic acid, R is at least 40% SO_3^- , R' and R'' are both SO_3^- or one is hydrogen and the other is 5-10% SO_3^- in glucuronic acid and 10-15% SO_3^- in iduronic acid, n is an integer from 3 to 15, with a mean molecular weight from approximately 4,000 to approximately 8,000.

50. Pharmaceutical composition according to anyone of claims 48 and 49, characterized in that said LMW-epiK5-amine-O-versulfate is consisting of a chain mixture in which the preponderant species has the formula II'a



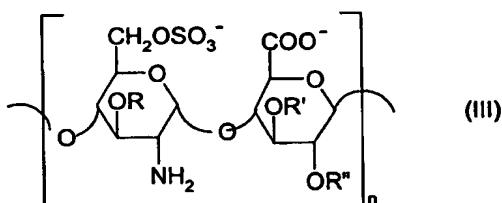
in which p is a integer from 4 to 8, R, R' and R" are as defined above, the degree of sulfation is from 3.55 to 4 and the corresponding cation is pharmaceutically acceptable.

51. Pharmaceutical composition according to claim 50, characterized in that said preponderant species is a compound of formula II'b



in which R, R' and R" are hydrogen or SO_3^- , X'' is OH or OSO_3^- , m is 4, 5 or 6, the uronic units are 40-60% consisting of iduronic acid, for a degree of sulfation from 3.55 to 4, the iduronic units being present alternately, starting with a glucuronic or iduronic unit, and the corresponding cation is one pharmaceutically acceptable ion.

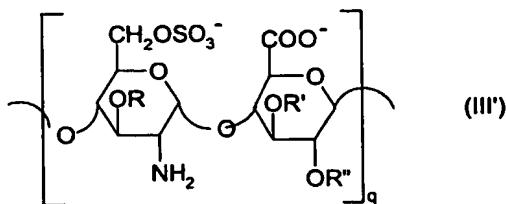
52. Pharmaceutical composition according to claim 45 including, as one of its active ingredients, a K5-amine-O-versulfate-derivative consisting of a chain mixture in which at least 90% of said chains have the formula III



in which n is a integer from 2 to 100, R, R' and R" are hydrogen or SO_3^- , the degree of sulfation is at least 2.2, and the corresponding cation is

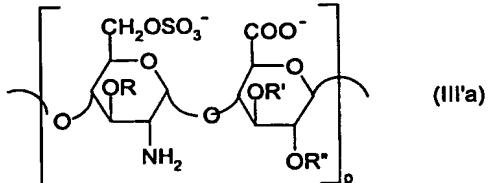
pharmaceutically acceptable.

53. Pharmaceutical composition according to claim 52, characterized in that said active ingredient is a LMW-K5-amine-O-oversulfate consisting of a chain mixture in which at least 90% of said chains have the formula III'



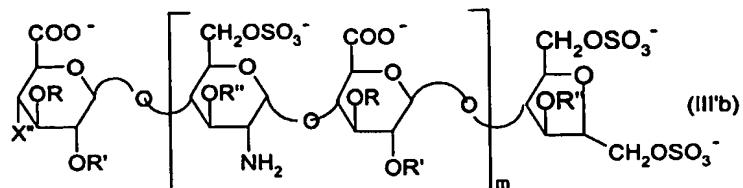
in which q is a integer from 2 to 20, R, R' and R'' represent hydrogen or an SO_3^- group for a sulfation degree of at least 2.2.

54. Pharmaceutical composition according to claim 53, characterized in that said LMW-K5-amine-O-oversulfate is consisting of a chain mixture in which the preponderant species has the formula III'a



in which p is a integer from 4 to 8, R, R' and R'' are as defined above, the degree of sulfation is from 2.2 to 3.

55. Pharmaceutical composition according to claim 50, characterized in that said preponderant species is a compound of formula III'b



in which R, R' and R'' are hydrogen or SO_3^- , X'' is OH or OSO_3^- , for a degree of sulfation from 2.2 to 3, m is 4, 5 or 6 and the corresponding

cation is one pharmaceutically acceptable ion.

56. Pharmaceutical composition according to anyone of claims from 45 to 55, characterized in that said pharmaceutically acceptable salt or cation is sodium, potassium, calcium, magnesium or zinc.

57. Pharmaceutical composition according to anyone of claims from 45 to 56, characterized in that it is in the form of cream, ointment, liniment, gel, foam, balsam, vaginal pessary, suppository, solution or suspension for local administration.

58. A pharmaceutical composition containing, as one of its active ingredients, a pharmacologically active amount of a Imw-(epi)K5-N-sulfate basically free of acetyl groups, or of one of its pharmaceutically acceptable salts, in mixture with a pharmaceutical excipient.

59. A cosmetic composition containing an effective amount of a Imw-(epi)K5-N-sulfate according to anyone of claims from 1 to 10 and from 25 to 37, in which said salt or cation is pharmaceutically acceptable, in mixture with a cosmetic excipient.